REMARKS

A. Status of the claims

Claims 1 and 3-19 are pending in this application. Applicants have canceled claim 3, amended claims 1 and 4-6, and added new claims 20-46 to identify the specific mutants or variants and peptides of the present invention as suggested by the Examiner. Support for the term non-proteolytic cysteine protease can be found in the specification on page 4, line 25 and page 7, line 3. Support for the specific peptides, which correspond to antigenic peaks, can be found in the specification on page 30 and the Sequence Listing. Applicants have enclosed as Appendix A a marked version of the claims illustrating the amendments contained herein. For the convenience of the Examiner, Applicants have also enclosed in Appendix B a copy of all pending claims containing the amendments herein. Applicants assert that no new matter is added.

B. The claims are enabled.

In the Office Action, the Examiner rejected claims 3-19 under 35 U.S.C. 112, first paragraph because the specification, while being enabling for specific mutants does not reasonably provide enablement for any mutants thereof or synthetic peptides thereof. Applicants respectfully traverse.

In specific embodiments, the present invention is drawn to non-proteolytic cysteine proteases. In order to advance the prosecution of the present invention, Applicants have amended the claims to clarify the specific embodiments of the present invention, *e.g.*, a non-proteolytic cysteine protease. Yet further, Applicants have also included the specific variants or mutants that are disclosed in the specification, for example, Figure 8 and pages 32-35.

In light of the above arguments and the amendments, Applicants assert that the claims are enabled and request withdrawal of the 112, first paragraph rejection.

C. The claims are definite.

The Office Action has rejected claims 1 and 3-19 under 35 U.S.C. 112, second

paragraph as being indefinit for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants traverse.

Applicants have amended the claims to delete the acronyms SPEB2-39 and the terms "mutants thereof" and "synthetic peptides thereof". Thus, in light of the amendments contained herein, Applicants respectfully request withdrawal of the 112, second paragraph rejection.

D. The claims are novel.

The Office Action has rejected claims 1 and 3-4 under 35 U.S.C. 102b as being anticipated by Hauser et al. The Office Action asserts that the cysteine protease taught in Hauser et al is identical to the cysteine protease claimed in the present invention. The Office Action also asserts that the intended usage and vaccine language does not carry any patentable weight. Applicants traverse.

Applicants assert that the amendments contained herein clearly distinguishes the cysteine protease of the present invention from that of Hauser et al. In addition to the fact that the claimed cysteine proteases are non-proteolytic, Applicants selected mutants that are antigenic for which there is no teaching or suggestion from Hauser to select the claimed mutants. Thus, Applicants assert that the claims as contained herein are clearly different and are not anticipated by Hauser et al.

In light of the amendments contained herein and the arguments, Applicants respectfully request withdrawal of the 102 rejection.

E. Claim 5 is non-obvious.

The Office Action has rejected claim 5 under 35 U.S.C. 103 as being obvious in view of Hauser et al. and Abe et al. Applicants traverse.

Claim 5 is **not** *prima facie* obvious because there is no suggestion to combine the references and there is no reasonable expectation of success as the references and the common art teach away from the claimed invention (*In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed Cir. 1992), *W. L.*

Gore & Assoc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)).

Applicants assert that Hauser et al does not teach or suggest the use of non-proteolytic cysteine proteases as a vaccine. Yet further, Abe et al does not teach cysteine proteases as vaccines or methods of vaccination using cysteine proteases. Abe et al states that SPE B is a toxin. Abe specifically describes that SPE B acts as a superantigen, which contributes to its function as a toxin. This toxic mechanism involves stimulation of immune cells that contribute to and accentuate the deleterious effects of the toxin. (See p.3750). This teaching does not provide a suggestion of the suitability of SPE B as an immunizing agent. In the absence of any motivation or suggestion, one skilled in the art would not combine the teachings of Abe et al with the teachings of Hauser. Certainly, even if combined, the cited references do not teach the vaccine employing the claimed mutants.

Thus, in view of the above arguments and the amendments contained herein, Applicants respectfully request the Examiner to reconsider the rejection of Claim 5.

F. Claims 6-17 are non-obvious.

The Office Action has rejected Claims 6-17 over Fischetti et al., and Kehoe in view of Hauser et al. and in further view of Abe et al. The Office Action states that motivation to combine the references would be derived from the knowledge that conserved cysteine proteases are found in all isolates of Streptococcus and to the general suggestion by Kehoe that a multivalent vaccine would be more effective. However, the addition references (Kehoe and Fischetti) do not cure the deficiencies of Hauser and Abe, as discussed above. Applicants traverse.

Applicants assert that the claimed invention as a whole, is not obvious to one of ordinary skill in the art because there would not be a reasonable expectation of success for combining the references (*W. L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)). In fact, Applicants note that the claimed invention is directed to a vaccine employing non-proteolytic mutants of a cysteine protease and a method of immunizing mammals using such a vaccine. Thus, the present invention involves more than a purified, active cysteine protease.

Applicants assert that there is no reasonable expectation of success based upon the references cited by the Office. A teaching regarding a proteolytically-active, cysteine protease does not provide any teaching for the claimed vaccine or any vaccine since the skilled artisan would not administer a native form of the cysteine protease as a vaccine.

The Office relies on Kehoe as being the reference that suggests or provides the motivation for one of skill in the art to combine the references. However, Kehoe is a review article that reviews prior studies related to the development of group A streptococcal vaccines using M protein which is different than the cysteine protease of the present invention. Clearly, Kehoe as a primary reference and its secondary references do not suggest nor do they teach obtaining a non-proteolytic antigen.

Thus, in light of these facts, it is clear that the present invention is non-obvious in view of Fischetti et al., and Kehoe in view of or Hauser et al. and in further view of Abe et al. Applicants respectfully request withdrawal of the 103 rejection.

CONCLUSIONS

Entry of the amendments to the claims before examination of the application is respectfully requested. Claim 3 has been deleted and Claims 1 and 4-6 have been amended. Claims 20-46 have been added. The original application contained 17 claims of which 2 were independent. The amendment added 35 claims of which there are 9 independent claims in excess of 3. Thus, Applicants believe that the amount of $1350.00 in fees are due. Please charge these fees to Account No. 06-2375, under Order No. 09507112. If any additional fees are due, please charge the additional fees to Account No. 06-2375, under Order No. 09507112, from which the undersigned is authorized to draw.

In light of the amendments and remarks, Applicants respectfully request that the rejections to the claims be reversed and a Letter Patent be issued on the application. If there are any questions regarding this Amendment and Response or the application in general, please do not hesitate to contact the undersigned.

Dated: July 30, 2001

Respectfully submitted,

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Appendix A

Version With Markings to Show Changes Made

1. (Amended three four times) A vaccine comprising:

a physiologically acceptable non-toxic vehicle containing a purified non-proteolytic cysteine protease, which confers immunity to a mammal against Group A streptococcal infection, ~~selected from the group consisting of SPEB2, SPEB3, SPEB4, SPEB5, SPEB6, SPEB7, SPEB8, SPEB9, SPEB10, SPEB11, SPEB12, SPEB13, SPEB14, SPEB15, SPEB16, SPEB17, SPEB18, SPEB19, SPEB20, SPEB21, SPEB22, SPEB23, SPEB24, SPEB25, SPEB26, SPEB27, SPEB28, SPEB29, SPEB30, SPEB31, SPEB32, SPEB33, SPEB34, SPEB35, SPEB36, SPEB37, SPEB38, and SPEB39,~~ wherein said cysteine protease comprises at least one amino acid substitution in the catalytic domain and said amino acid substitution occurs at the amino acid position selected from the group consisting of Lys145, Gln185, Cys192, His340, Asn356 and Trp357.

4. (Amended twice) The vaccine of claim 1 ~~or claim 3~~, wherein said infection is selected from the group consisting of pharyngitis, tonsillitis, skin infections, acute rheumatic fever, scarlet fever, post-streptococcal glomerulonephritis, and toxic-shock-like syndrome.

5. (Amended twice) The vaccine of claim 1 ~~or claim 3~~, further comprising a purified streptococcal M protein antigen.

6. (Amended twice) A method of immunizing mammals comprising:

administering to a mammal a vaccine comprising, a purified non-proteolytic cysteine ~~protease, synthetic peptide thereof, or mutant thereof,~~ in an amount sufficient to confer immunity to a Group A streptococcal infection, wherein said cysteine protease comprises at least one amino acid substitution in the catalytic domain and said amino acid substitution occurs at the amino acid position selected from the group consisting of Lys145, Gln185, Cys192, His340, Asn356 and Trp357.

Appendix B

Claims pending as of July 30, 2001

1. A vaccine comprising:

a physiologically acceptable non-toxic vehicle containing a purified non-proteolytic cysteine protease, which confers immunity to a mammal against Group A streptococcal infection, wherein said cysteine protease comprises at least one amino acid substitution and said amino acid substitution occurs at the amino acid position selected from the group consisting of Lys145, Gln185, Cys192, His340, Asn356 and Trp357.

4. The vaccine of claim 1, wherein said infection is selected from the group consisting of pharyngitis, tonsillitis, skin infections, acute rheumatic fever, scarlet fever, post-streptococcal glomerulonephritis, and toxic-shock-like syndrome.

5. The vaccine of claim 1 further comprising a purified streptococcal M protein antigen.

6. A method of immunizing mammals comprising:

administering to a mammal a vaccine comprising, a purified non-proteolytic cysteine in an amount sufficient to confer immunity to a Group A streptococcal infection, wherein said cysteine protease comprises at least one amino acid substitution and said amino acid substitution occurs at the amino acid position selected from the group consisting of Lys145, Gln185, Cys192, His340, Asn356 and Trp357.

7. The method of claim 6, wherein said vaccine is given by parenteral administration.

8. The method of claim 7, wherein said parenteral administration is selected from the group consisting of subcutaneous administration and intramuscular administration.

9. The method of claim 6, wherein said vaccine is administered orally.

10. The method of claim 6, wherein said infection is selected from the group consisting of pharyngitis, tonsillitis, skin infections, acute rheumatic fever, scarlet fever, post-streptococcal glomerulonephritis, sepsis, and toxic-shock-like syndrome.

11. The method of claim 6, wherein said vaccine is administered in multiple doses.

12. The method of claim 6 further comprising:

administering to the mammal a purified streptococcal M protein antigen.

13. The method of claim 12, wherein said vaccine is given by parenteral administration.

14. The method of claim 13, wherein said parenteral administration is selected from the group consisting of subcutaneous administration and intramuscular administration.

15. The method of claim 12, wherein said vaccine is administered orally.

16. The method of claim 12, wherein said infection is selected from the group consisting of pharyngitis, tonsillitis, skin infections, acute rheumatic fever, scarlet fever, post-streptococcal glomerulonephritis, sepsis, and toxic-shock-like syndrome.

17. The method of claim 12, wherein said vaccine is administered in multiple doses.

18. The vaccine of claim 1, wherein said mammal is a human.

19. The method of claim 6, wherein said mammal is a human.

20. The vaccine of claim 1, wherein said amino acid substitution is selected from the group consisting of Lys145→Ala145, Cys192→Ala192, Cys192→Ser192, His340→Ala340, Gln185→Ala185, Asn356→Ala356 and Trp357→Ala357.

21. The method of claim 6, wherein said amino acid substitution is selected from the group consisting of Lys145→Ala145, Cys192→Ala192, Cys192→Ser192, His340→Ala340, Gln185→Ala185, Asn356→Ala356 and Trp357→Ala357.

22. The vaccine of claim 20, wherein said amino acid substitution is Cys192→Ala192 or Cys192→Ser192.

23. The method of claim 21, wherein the amino acid substitution is Cys192→Ala192 or Cys192→Ser192.

24. The vaccine of claim 1, wherein said amino acid substitution occurs at Lys145.

25. The vaccine of claim 1, wherein said amino acid substitution occurs at Cys192.

26. The vaccine of claim 1, wherein said amino acid substitution occurs at Gln185.

27. The vaccine of claim 1, wherein said amino acid substitution occurs at Asn356.

28. The vaccine of claim 1, wherein said amino acid substitution occurs at Trp357.

29. The method of claim 6, wherein said amino acid substitution occurs at Lys145.

30. The method of claim 6, wherein said amino acid substitution occurs at Cys192.

31. The method of claim 6, wherein said amino acid substitution occurs at His340.

32. The method of claim 6, wherein said amino acid substitution occurs at Gln185.

33. The method of claim 6, wherein said amino acid substitution occurs at Asn356.

34. The method of claim 6, wherein said amino acid substitution occurs at Trp357.

35. A vaccine comprising a cysteine protease peptide, wherein said peptide is selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13 and SEQ ID NO: 14.

36. A method of immunizing mammals comprising administering to a mammal a vaccine comprising a cysteine protease peptide, wherein said peptide is selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13 and SEQ ID NO: 14.

37. An isolated peptide comprising an amino sequence of SEQ ID NO: 8.

38. An isolated peptide comprising an amino sequence of SEQ ID NO: 9.

39. An isolated peptide comprising an amino sequence of SEQ ID NO: 10.

40. An isolated peptide comprising an amino sequence of SEQ ID NO: 11.

41. An isolated peptide comprising an amino sequence of SEQ ID NO: 12.

42. An isolated peptide comprising an amino sequence of SEQ ID NO: 13.

43. An isolated peptide comprising an amino sequence of SEQ ID NO: 14.

44. A vaccine comprising a purified non-proteolytic cysteine protease, which confers immunity to a mammal against Group A streptococcal infection, wherein said cysteine protease comprises at least one amino acid substitution and said amino acid substitution occurs at the amino acid position selected from the group consisting of Lys145, Gln185, Cys192, His340, Asn356 and Trp357.

45. A method of immunizing mammals comprising administering to a mammal a vaccine of claims 1, 5, 20, 22, 24, 25, 26, 27, 28 or 44 in an amount sufficient to confer immunity to a Group A streptococcal infection.

46. The method of claim 45, the mammal is human.